REMARKS

Amendments in the specification

A paragraph is added after the first paragraph of the specification to cross-reference the present application to a co-pending application having related subject matter. The publication of that co-pending application, US 2005/0197385, is already of record in the present application, by IDS submitted on November 28, 2007.

Amendments in the claims

Following amendment as requested herein, Claims 1 and 3–20 are pending in the present application, of which Claims 19 and 20 are presently withdrawn from consideration. Claim 2 is canceled by the present amendment.

Claim 1 is amended to incorporate the limitation of Claim 2, which is canceled without prejudice herein. Claim 1 is also amended to more clearly recite two steps in the claimed method: an identifying step and an administering step. The administering step was explicit in the body of Claim 1 prior to amendment herein; the step of "identifying a subject (i) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease, or (ii) with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease, said symptoms being rigor, resting tremor, bradykinesia and postural instability" was implicit in now-canceled Claim 2. The specification as filed is replete with disclosure as to how such a subject can be identified; see, for example, paragraphs **[0039]**–**[0054]** of the English-language translation of the specification as filed. Opportunity is taken, while importing the limitation of Claim 2 to Claim 1, to modify the wording for clarity. Support for the amended wording of the phrase "with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease, said symptoms being rigor, resting tremor, bradykinesia and postural instability" is also found in the English-language translation of the specification as filed, at least at paragraph **[0046]**.

Claim 3 is amended to align the wording more closely with that of herein-amended Claim 1.

Claim 4 is amended as to dependency only, this amendment being necessary in view

of cancellation of Claim 2 herein.

Claim 6 is amended to correct a spelling error. The correct spelling of "methoxyphenyl" is seen in the English-language translation of the specification as filed, at paragraph **[0026]**.

Opportunity is taken to correct deficiencies of grammar throughout the claims and, where necessary, to re-word in better accordance with standard U.S. claim-drafting practice.

No new matter is introduced by amendment of the claims herein.

RESPONSE TO OFFICE ACTION DATED FEBRUARY 19, 2009

1. Restriction requirement

Applicant's traverse of the restriction requirement between original Groups I and II (Claims 1–18) has been found persuasive and the requirement is withdrawn. Original Groups III and IV are likewise rejoined.

By the present Action, restriction is required between new Group I (original Groups I and II rejoined) and new Group II (original Groups III and IV rejoined). Applicant elects not to traverse this requirement and agrees with the Examiner's decision to examine new Group I.

However, Applicant respectfully disagrees with the Examiner's remark (Action, bottom of p. 4) that the kit of new Group II "is used specifically for diagnosis and treatment of Parkinson's disease, not prevention" (emphasis added). The whole thrust of the present invention, including the kit embodiments thereof, is that administration of a compound as defined herein is useful for preventive treatment of Parkinson's disease; the role of the diagnostic component of the kit is to identify a suitable subject for such treatment by testing for predisposing risk factors and/or for dopaminergic neuron loss before the disease progresses to the stage of exhibiting two or more cardinal symptoms.

2. Rejection under 35 U.S.C. §112, first paragraph

Claims 1–18 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enabling support in the specification. This rejection is moot as to now-canceled Claim 2 and is respectfully traversed with respect to Claims 1 and 3–18.

The alleged lack of enablement applies to preventive treatment of Parkinson's disease, treatment (presumably of already clinically diagnosed Parkinson's disease) having been found

enabled (Action, p. 6). The presently rejected claims are particularly drawn to preventive treatment as defined in the specification, it being acknowledged in the present specification (see, for example, paragraph **[0008]** thereof) that treatment of symptoms with the present compounds after clinical diagnosis of Parkinson's disease forms part of the state of the art.

The Action attempts an analysis using the Wands factors (MPEP 2164.01(a)). Taking each of these factors in turn, Applicant responds as follows.

Nature of the invention. Applicant accepts that there is some complexity in the present invention, but it is not complexity of a form that would require undue experimentation for one of ordinary skill to practice the invention. Applicant is unclear as to the meaning of the statement that the nature of the invention is "extremely complex in that it encompasses the actual prevention of a neurodegenerative disease such that the subject treated with rotigotine does not contract Parkinson's disease" (Action, p. 7, emphasis in original). The specification clearly teaches that rotigotine reduces or arrests dopaminergic neuron loss. If rotigotine is administered before dopaminergic neuron loss begins or progresses too far, for example where such loss is less than 50%, it is not impossible that neuron loss could be stabilized at such a level more or less indefinitely, with the result that a clinical diagnosis of Parkinson's disease is never made (typically clinically evident Parkinson's disease is seen only when 70–80% dopaminergic neuron loss has been suffered – see specification, paragraph **[0003]**, citing Becker (2002) and Hornykiewicz (2001)).

Applicant stresses, however, that the term "preventive treatment" as used in the present application is not limited to (although it does encompass) a degree of neuroprotection sufficient to totally prevent any onset of clinically evident Parkinson's disease. The present specification, at paragraph **[0055]**, clearly defines "prevention" and "preventive treatment" of Parkinson's disease as encompassing not only preventing but delaying appearance or significant development of motor symptoms of the disease.

Such complexity as exists, therefore, does not require undue experimentation. So long as a subject is identified having no more than a moderate degree of dopaminergic neuron loss, or having one or more predisposing risk factors for Parkinson's disease (the specification is replete with teaching as to how this can be done), one of skill in the art can readily administer rotigotine in accordance with the present disclosure.

Breadth of claims. The fact that dopaminergic neuron loss (reduction or arresting of which underlies the claimed preventive treatment) has a multiplicity of causes does not, contrary to the present Action (p. 7), result in excessively broad claims. There is no suggestion that administration of rotigotine can address such causes of neuron loss, including mutations or combination of mutations. What rotigotine has been shown to do is reduce neuron loss (*i.e.*, provide neuroprotection), not prevent mutations. The MPTP model used in the present Examples to demonstrate neuroprotective properties of rotigotine is applicable to a broad range of neuronal cell death pathways, thus is not specific to any one cause of neuron loss. See, for example, Dawson & Dawson (2002) Nature Neurosci. Suppl. 5:1058–1061, of record in the present application, which states at p. 1059, col. 1, first paragraph:

> Most, if not all, known neuronal cell death pathways have been implicated in the MPTP model and hence PD [Parkinson's disease], including excitotoxicity, toxicity from reactive oxygen species ..., apoptosis (caspase-dependent and -independent pathways), necrosis and glial (inflammation)-induced injury.

Applicant also respectfully disagrees with the assertion (Action, passage bridging pp. 7–8) that preventive treatment administered at all preclinical stages including undetectable stages renders the claims excessively broad. Two situations are excluded by the present claims: (1) Parkinson's disease already clinically evident through presence of two or more cardinal symptoms; and (2) no detectable symptoms coupled with no increased risk factors. The patient population that remains, as identified in step (a) of Claim 1 as amended herein, is a well defined population that one of ordinary skill in the art can readily identify based on the present disclosure. No undue experimentation is involved as a result of the breadth of the present claims.

Guidance of the specification. The statement (Action, p. 8, emphasis in original) that "[a]ll of the guidance provided by the specification is directed towards treatment rather than prevention of Parkinson's disease" could hardly be more wrong. Virtually the entire specification is directed to a method in which rotigotine or a salt or prodrug thereof is administered to a subject who does not have the cardinal symptoms of Parkinson's disease but who is at risk of developing the disease or has early symptoms. As emphasized above, use of rotigotine to treat Parkinson's disease in subjects already having the cardinal symptoms is the

current state of the art and is not the subject of the present invention.

The Action (p. 8) also asserts that guidance in the specification as to how one would administer the compounds is minimal. On the contrary, paragraphs **[0059]–[0065]** of the specification, and art cited therein, provide ample guidance as to how this can be done. Based on this teaching, no undue experimentation is required by the person of ordinary skill in the art.

Working examples. The working examples are not directed to "treatment rather than prevention" of Parkinson's disease (Action, p. 8). The examples use the MPTP model, a model accepted in the art as predictive of neuroprotective properties of drugs (see Dawson & Dawson (2002), *supra*). According to Dawson & Dawson, at p. 1059, col. 1 thereof, "neuroprotective agents need to be given prophylactically in the MPTP model" (emphasis added). In Embodiments 3 and 4 of the present specification, no indication is given that the mice "displayed clinical manifestations of neurodegeneration" as asserted in the Action (p. 8). In both Embodiments, MPTP-treated mice exhibited 50–60% neuron loss, a level consistent with a subject not (or not yet) having clinically evident Parkinson's disease.

As the working examples used a well-established prophylactic model and the degree of neuron loss was indicative of a prediagnostic stage of the disease, Applicant submits that the data are (contrary to the assertion in the Action) sufficient to demonstrate preventive action of rotigotine.

State of the art. Applicant agrees with the Examiner's assessment of the state of the art as "underdeveloped" with respect to prevention of neurodegenerative disorders. The admission (Action, p. 8, emphasis in original) that "[i]n particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to prevent development of Parkinson's disease" is noted. Additionally, the remark of Tuite *et al.* (2003) Expert Opin. Invest. Drugs 12(8):1335–1352, paraphrased in the Action (passage bridging pp. 9–10) as teaching "that although effective, the overall impact of symptomatic medications is limited in the long run, since there is no means to prevent Parkinson's disease (*i.e.*, preventive therapy) or restore lost dopamine neurons (*i.e.*, restorative therapy)" is broadly in line with Applicant's position that the present invention provides a breakthrough in preventive treatment. (Applicant does not rule out

restorative therapy; however, preventive treatment of Parkinson's disease does not require restoration of lost neurons, only a slowing or arresting of further neuron loss, as evidenced in the present specification.)

The Action cites Stern (2004) Ann. Neurol. 56:169–171 as confirming the teaching of the present specification that there is a lengthy preclinical phase of Parkinson's disease in which neurodegeneration proceeds without emergence of clinically recognizable symptoms, and as raising economic, legal and ethical issues relating to preclinical diagnosis in absence of "something to offer affected individuals". (Contrary to the statement in the Action at p. 9, line 15, Stern does not define that "something to offer" as a "cure".)

Applicant notes, first, that such economic, legal and ethical issues do not result in lack of enablement for the person of ordinary skill, such enablement being a question of technical capability. Sufficient teaching is provided in the present specification and in the art to enable the ordinarily skilled person to make a preclinical diagnosis; economic, legal and ethical considerations have no place in that analysis. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP 2164.01, citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d, 1217 (Fed. Cir. 1988).

Applicant further notes that the statement attributed to Stern (Action, p. 9, lines 16–18) that "although numerous compounds prevent cell loss in laboratory models of neurodegeneration, demonstrating their effect in acceptable clinical trials has been a challenge" is taken out of context. This remark by Stern, read in context, will be seen to carry the implicit rider "until now"; it is immediately preceded by the suggestion that "it is now conceivable to design a clinical trial in which the end point of an intervention can be the onset of clinical PD", and immediately followed by the statement that "[f]ollowing a cohort of treated and untreated preclinical PD patients to the onset of PD may now be feasible" (Stern, p. 170, col. 2, lines 7–14). In other words, Stern proposes that a successful result in laboratory animals can now be confirmed by appropriate clinical testing.

Predictability of the art. Applicant agrees with the implication in the Action (p. 10) that preventive treatment of Parkinson's disease is an unpredictable art area, but takes issue with the remark that practicing the claimed invention is somehow unpredictable because of an

alleged lack of significant guidance with regard to prevention. As pointed out above (see under "guidance of the specification" and "working examples"), the present specification is replete with guidance as to how the preventive treatment of the claims can be practiced.

Amount of experimentation necessary. Contrary to the assertion in the Action (passage bridging pp. 10–11), one of ordinary skill does not have to "envision" a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration and appropriate animal system to test, as all of these are laid out in the specification. It is not "likely" that such a test would be unsuccessful, there being every reason to suppose that what worked for the present inventors would work for the ordinarily skilled person repeating the test. No undue amount of experimentation is necessary to practice the invention as presently claimed, based on the disclosure in the present specification.

In summary, a correct analysis of the *In re Wands* factors leads to the conclusion that a method of preventive treatment of Parkinson's disease as set forth in the instant claims is fully enabled under 35 U.S.C. §112, first paragraph. Withdrawal of the present rejection is respectfully requested.

3. Rejection under 35 U.S.C. §102(b) over Tuite

Claims 1, 5–14, 17 and 18 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tuite & Riss (2003) Expert Opin. Invest. Drugs 12(8):1335–1352 (herein "Tuite"). This rejection is respectfully traversed.

Tuite reviews a clinical trial of rotigotine administered transdermally in 316 patients with early stage Parkinson's disease. These patients were therefore not subjects as identified in the method of Claim 1 as amended herein. The subject according to Claim 1 has not (or not yet) been diagnosed with Parkinson's disease, at least three of the cardinal symptoms of rigor, resting tremor, bradykinesia and postural instability being absent or being present only to a rudimentary or partial degree.

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. That is not the case here. Tuite does not disclose, either expressly or inherently, identifying a subject (i) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's

disease, or (ii) with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease. Claim 1 as amended herein is therefore novel over Tuite.

With particular reference to Claim 14, the Examiner argues that the limitation of "a dopaminergic cell loss in the substantia nigra of less than 60%" as recited therein renders the claim inherently anticipated by Tuite as evidenced by Becker *et al.* (2002) J. Neurol. 249(Suppl. 3):III/40–III/48 (herein "Becker"), cited as evidence that "approximately 60% of the nigrostriatal neurons of the substantia nigra are degenerated before neurologists can establish the diagnosis" (Action, p. 12, lines 18–20).

The alleged finding of inherent anticipation fails for at least three reasons.

1. Claim 14 embodies all the limitations of Claim 1 from which it depends and is accordingly novel for at least the same reasons that Claim 1 is novel. The subject identified according to Claim 14 does not have a diagnosis of Parkinson's disease (because of the dependency of Claim 14 from Claim 1). Thus even if, *arguendo*, Becker is read as teaching that a patient with, say, 59% (*i.e.*, "approximately 60%") dopaminergic cell loss could have a clinical diagnosis of Parkinson's disease, the particular subject treated according to Claim 14 is not such a patient.
2. The assertion in the Action (p. 12, lines 20–22) that "[a]ccordingly, all the individuals in the study recited by Tuite who had early stages of PD inherently had approximately 60% loss of the substantia nigra" is logically absurd. Many could have had much greater than 60% loss, thus the limitation of "a dopaminergic cell loss in the substantia nigra of less than 60%" (emphasis added) in Claim 14 does not necessarily follow (as required for a showing of inherent anticipation) from the teaching of Becker.
3. It is noted, as admitted in the present Action at p. 17, lines 15–20, that International Patent Publication No. WO 02/31499 (herein "Double") states that in classical or idiopathic Parkinson's disease at least 65% of dopaminergic neurons in the substantia nigra are lost prior to clinical onset typified by the motor symptom triad of tremor, rigidity and bradykinesia.

For at least these reasons, the subject treated according to Claim 14 is not inherently found in the study reviewed by Tuite.

Like Claim 14, Claims 5–13, 17 and 18 depend from and incorporate all limitations of Claim 1 and are accordingly novel over Tuite for at least the same reasons that Claim 1 is novel. Withdrawal of the present rejection under 35 U.S.C. §102(b) over Tuite is respectfully requested.

4. Rejection under 35 U.S.C. §102(b) over Parkinson Study Group

Claims 1 and 5–18 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Parkinson Study Group (2003) Arch. Neurol. 60:1721–1728 (referenced in the Action as "Shoulson"). This rejection is respectfully traversed.

Parkinson Study Group reports a clinical trial of rotigotine applied transdermally in 242 patients with early Parkinson's disease. These patients were therefore not subjects as identified in the method of Claim 1 as amended herein. The subject according to Claim 1 has not (or not yet) been diagnosed with Parkinson's disease, at least three of the cardinal symptoms of rigor, resting tremor, bradykinesia and postural instability being absent or being present only to a rudimentary or partial degree.

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. That is not the case here. Parkinson Study Group does not disclose, either expressly or inherently, identifying a subject (i) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease, or (ii) with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease. Claim 1 as amended herein is therefore novel over Parkinson Study Group.

With particular reference to Claim 14, the Examiner argues that the limitation of "a dopaminergic cell loss in the substantia nigra of less than 60%" as recited therein renders the claim inherently anticipated by Parkinson Study Group as evidenced by Becker, cited as evidence that "approximately 60% of the nigrostriatal neurons of the substantia nigra are degenerated before neurologists can establish the diagnosis" (Action, p. 14, lines 8–10). The alleged finding of inherent anticipation fails for the same reasons set forth above in relation to

Tuite, which need not be repeated here.

Like Claim 14, Claims 5–13 and 15–18 depend from and incorporate all limitations of Claim 1 and are accordingly novel over Parkinson Study Group for at least the same reasons that Claim 1 is novel. Withdrawal of the present rejection under 35 U.S.C. §102(b) over Parkinson Study Group ("Shoulson") is respectfully requested.

5. Rejection under 35 U.S.C. §103(a) over Tuite as evidenced by Becker in view of Double and Guttman

Claims 1–18 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tuite as evidenced by Becker, in view of Double and Guttman *et al.* (2003) Can. Med. Assoc. J. 168:293–301 (herein "Guttman"). This rejection is moot with respect to now-canceled Claim 2 and is respectfully traversed with respect to Claims 3–18.

As shown above, the primary reference, Tuite, even as evidenced by Becker, fails to teach administration of rotigotine to a subject identified as recited in Claim 1, *i.e.*, a subject (i) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease, or (ii) with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease. Guttmann (cited in the Action apparently for alleged relevance to dependent Claim 4) fails to identify such a subject, or to suggest identifying such a subject, for treatment. Double provides a method for detecting preclinical Parkinson's disease in an individual based on a positive test result for an indicator of neuromelanin release, but does not appear to teach or suggest that such an individual is a suitable case for treatment with a dopamine agonist such as rotigotine or other compound of the formula set forth in Claim 1. Double instead proposes treatment of a positive-testing subject including "administering a therapeutically effective amount of at least one of the following: antioxidants, iron chelators, nonamine [*sic*; monoamine?] oxidase inhibitors, apoptosis inhibitors, growth factors, dopamine receptor inhibitors, endogenous enzymes which protect against oxidative damage such as glutathione, superoxide dismutase and catalase, inhibitors of excitatory damage, zonisamide, benzamide compounds, ethanesulfonyl-piperidine derivatives, or a combination thereof" (Double, p. 3, lines 24–30, emphasis added).

For brevity herein, administration of an anti-parkinsonism drug (in the present

instance rotigotine or a salt or prodrug thereof) to a subject lacking at least three of the four cardinal symptoms of Parkinson's disease, but in a prediagnostic phase of the disease or at risk for developing the disease, is referred to as "prophylactic" administration. This use of the term "prophylactic" is consistent with the meaning of the term as used in the present specification as filed, for example at p. 6, line 26.

The question at the heart of the present rejection is whether it would have been obvious at the time of the present invention to administer rotigotine, known in the art for treatment of symptoms of clinically evident Parkinson's disease (see, for example, the present specification as filed at p. 3, lines 5–34, as well as disclosure by Tuite of administration of rotigotine providing improvement in motor symptoms), prophylactically to a subject in a prediagnostic phase of the disease as recognized, for example, by Becker or Double.

A combination of Tuite with any or all of the secondary references cited in the present Action (assuming motivation exists for such combination, which is not admitted herein) does not provide an apparent rationale for a person of ordinary skill to select and modify elements from the collective teachings to arrive at the present invention. See *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (an obviousness inquiry includes determining whether there was an apparent reason to combine the known elements in the fashion claimed).

In the present case, the ordinarily skilled person would have had to select rotigotine treatment as disclosed by Tuite and modify it to provide prophylactic therapy to subjects at risk or in prediagnostic phases of Parkinson's disease, such subjects being mentioned for example by Becker and Double. A rationale proposed in the present Action is that "[o]ne of ordinary skill in the art would promptly evaluate those patients at risk or in early stages of Parkinson's disease in order to avoid failing of [*sic*; failure in] treating Parkinson's disease at their advanced stage" (Action, p. 19, lines 19–21), it being known from Tuite that advanced-stage Parkinson's disease is not responsive to rotigotine therapy.

The art recognizes importance of neuroprotection before neuronal loss has progressed to the level of about 60% (Becker) or 65% (Double) at which clinical diagnosis can be established; however, a "missing link" is that, prior to the present invention, dopamine agonist compounds of the formula set forth in Claim 1, including rotigotine, were not known to

possess neuroprotective properties. Indeed Double, in an extensive list of classes of agent that can be used for neuroprotection, makes no mention of dopamine agonists, and even teaches away by proposing treatment with "dopamine receptor inhibitors". While Double might arguably supply a rationale to administer a known neuroprotective agent prophylactically in a subject as defined in present Claim 1, no such rationale exists for compounds defined therein, including rotigotine. Just because a drug is known to alleviate symptoms of a disease is no reason to believe it can slow, delay or prevent onset of that disease when administered prophylactically. More specifically, just because a drug (such as rotigotine) is known to alleviate symptoms of clinical Parkinson's disease is no reason to believe it can have neuroprotective properties when administered prophylactically.

Thus the Examiner's statement (Action, passage bridging pp. 19–20) that "an ordinarily skilled artisan would be motivated to develop a method of treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease" can only have been made (a) with failure to distinguish between early clinical Parkinson's disease (as treated in the Tuite art) and prediagnostic disease (as treated according to instant Claim 1); or (b) with impermissible hindsight, as neuroprotective properties of rotigotine are disclosed for the first time in Applicant's specification. To reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination. MPEP 2142.

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection. This standard has been sanctioned by *KSR*, *supra*, but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*,

emphasis added. As paraphrased in MPEP 2143.01.III, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

At the time of the present invention it could not have been predicted that rotigotine, although known to be effective in reducing symptoms of Parkinson's disease post-diagnosis, would be an effective prophylaxis for Parkinson's disease in subjects not yet having a diagnosis of Parkinson's disease, let alone in subjects at risk for the disease but exhibiting no symptoms.

First, the medical arts are notoriously unpredictable; this is certainly true in the area of prophylaxis. Unpredictability in the art is acknowledged in the present Action at p. 10, lines 7–10.

Second, such suggestion as to likely outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. Despite the many drugs that have been developed for treatment of symptoms of Parkinson's disease, it is true that, as admitted in the present Action (passage bridging pp. 8–9), there do not appear to be examples in the prior art wherein a compound similar to the compounds defined in instant Claim 1 has been administered to a subject to prevent development of Parkinson's disease; state-of-the-art treatment being aimed at controlling the symptoms. At least one of the secondary references applied in the present rejection emphasizes that "no therapies are proven to ... delay the progression of Parkinson's disease" (Guttman, p. 297, bottom of col. 1). A treatment algorithm provided by Guttman (p. 298) begins with "clinical diagnosis of Parkinson's disease", further confirming the absence of suitable therapies in the prediagnostic phase of the disease. Thus it cannot be said that, as of the date of the present invention, successful prophylaxis was a predictable outcome. Absent reasonable predictability of outcome, *prima facie* obviousness has not been established under the *KSR* standard.

For at least the reasons presented above, a case of *prima facie* obviousness cannot be sustained for Claim 1 over Tuite as evidenced by Becker, in view of Double and Guttman.

Each of Claims 3–18 depends from and incorporates all limitations of Claim 1. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 3–18 is non-obvious over the cited art for at least the same reasons that Claim 1 is

non-obvious. Withdrawal of the present rejection under 35 U.S.C. §103(a) over Tuite as evidenced by Becker, in view of Double and Guttman, is respectfully requested.

6. Rejection under 35 U.S.C. §103(a) over Parkinson Study Group as evidenced by Becker in view of Double and Guttman

Claims 1–18 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Parkinson Study Group (referred to in the present Action as "Shoulson") as evidenced by Becker, in view of Double and Guttman. This rejection is moot with respect to now-canceled Claim 2 and is respectfully traversed with respect to Claims 3–18.

As shown above, the primary reference, Parkinson Study Group, even as evidenced by Becker, fails to teach administration of rotigotine to a subject identified as recited in Claim 1, *i.e.*, a subject (i) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease, or (ii) with early symptoms of Parkinson's disease but not exhibiting, other than to a rudimentary or partial degree, at least three of four cardinal symptoms of Parkinson's disease. The relevance, or lack thereof, of Guttmann and Double to the present inquiry is as set forth in section 5 above and need not be repeated here.

The question at the heart of the present rejection is whether it would have been obvious at the time of the present invention to administer rotigotine, known in the art for treatment of symptoms of clinically evident Parkinson's disease (see, for example, the present specification as filed at p. 3, lines 5–34, as well as disclosure by Parkinson Study Group of administration of rotigotine providing improvement in motor symptoms), prophylactically to a subject in a prediagnostic phase of the disease as recognized, for example, by Becker or Double.

A combination of Parkinson Study Group with any or all of the secondary references cited in the present Action (assuming motivation exists for such combination, which is not admitted herein) does not provide an apparent rationale for a person of ordinary skill to select and modify elements from the collective teachings to arrive at the present invention. See *KSR, supra* (an obviousness inquiry includes determining whether there was an apparent reason to combine the known elements in the fashion claimed).

In the present case, the ordinarily skilled person would have had to select rotigotine treatment as disclosed by Parkinson Study Group and modify it to provide prophylactic

therapy to subjects at risk or in prediagnostic phases of Parkinson's disease, such subjects being mentioned for example by Becker and Double. A rationale proposed in the present Action is that "[o]ne of ordinary skill in the art would promptly evaluate those patients at risk or in early stages of Parkinson's disease in order to avoid failing of [*sic*; failure in] treating Parkinson's disease at their advanced stage" (Action, p. 24, lines 7–9), it being known from Parkinson Study Group that advanced-stage Parkinson's disease did not show statistically significant improvement with rotigotine therapy.

The art recognizes importance of neuroprotection before neuronal loss has progressed to the level of about 60% (Becker) or 65% (Double) at which clinical diagnosis can be established; however, a "missing link" is that, prior to the present invention, dopamine agonist compounds of the formula set forth in Claim 1, including rotigotine, were not known to possess neuroprotective properties. Indeed Double, in an extensive list of classes of agent that can be used for neuroprotection, makes no mention of dopamine agonists, and even teaches away by proposing treatment with "dopamine receptor inhibitors". While Double might arguably supply a rationale to administer a known neuroprotective agent prophylactically in a subject as defined in present Claim 1, no such rationale exists for compounds defined therein, including rotigotine. Just because a drug is known to alleviate symptoms of a disease is no reason to believe it can slow, delay or prevent onset of that disease when administered prophylactically. More specifically, just because a drug (such as rotigotine) is known to alleviate symptoms of clinical Parkinson's disease is no reason to believe it can have neuroprotective properties when administered prophylactically.

Thus the Examiner's statement (Action, p. 24, lines 10–13) that "an ordinarily skilled artisan would be motivated to develop a method of treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease" can only have been made (a) with failure to distinguish between early clinical Parkinson's disease (as treated in the Parkinson Study Group art) and prediagnostic disease (as treated according to instant Claim 1); or (b) with impermissible hindsight, as neuroprotective properties of rotigotine are disclosed for the first time in Applicant's specification. To reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person

of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination. MPEP 2142.

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection. This standard has been sanctioned by *KSR*, *supra*, but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*, emphasis added. As paraphrased in MPEP 2143.01.III, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

At the time of the present invention it could not have been predicted that rotigotine, although known to be effective in reducing symptoms of Parkinson's disease post-diagnosis, would be an effective prophylaxis for Parkinson's disease in subjects not yet having a diagnosis of Parkinson's disease, let alone in subjects at risk for the disease but exhibiting no symptoms.

First, the medical arts are notoriously unpredictable; this is certainly true in the area of prophylaxis. Unpredictability in the art is acknowledged in the present Action at p. 10, lines 7–10.

Second, such suggestion as to likely outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. Despite the many drugs that have been developed for treatment of symptoms of Parkinson's disease, it is true that, as admitted in the present Action (passage bridging pp. 8–9), there do not appear to be examples in the prior art wherein a compound similar to the compounds defined in instant Claim 1 has been administered to a subject to prevent development of Parkinson's disease; state-of-the-art treatment being aimed at controlling the symptoms. At least one of the secondary references applied in the present rejection emphasizes that "no therapies are

proven to ... delay the progression of Parkinson's disease" (Guttman, p. 297, bottom of col. 1). A treatment algorithm provided by Guttman (p. 298) begins with "clinical diagnosis of Parkinson's disease", further confirming the absence of suitable therapies in the prediagnostic phase of the disease. Thus it cannot be said that, as of the date of the present invention, successful prophylaxis was a predictable outcome. Absent reasonable predictability of outcome, *prima facie* obviousness has not been established under the *KSR* standard.

For at least the reasons presented above, a case of *prima facie* obviousness cannot be sustained for Claim 1 over Parkinson Study Group as evidenced by Becker, in view of Double and Guttman.

Each of Claims 3–18 depends from and incorporates all limitations of Claim 1. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 3–18 is non-obvious over the cited art for at least the same reasons that Claim 1 is non-obvious. Withdrawal of the present rejection under 35 U.S.C. §103(a) over Parkinson Study Group ("Shoulson") as evidenced by Becker, in view of Double and Guttman, is respectfully requested.

7. Non-statutory obviousness-type double patenting

Claims 1–18 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claim 15–24 of copending application Serial No. 11/060,997. The rejection is provisional because the allegedly conflicting claims have not yet been patented. The Examiner's statement that "[t]he subject matter claimed in the instant application ... would be covered by any patent granted on that copending application" (Action, p. 25) is not a conclusion that can be reliably drawn at the present time. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '997 application issues as a patent.

Claims 1, 5–13, 17 and 18 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 8, 11 and 14 of copending application Serial No. 10/593,964. The rejection is provisional because the allegedly conflicting claims have not yet been patented. The Examiner's statement that "[t]he subject matter claimed in the instant application ... would be covered by any patent

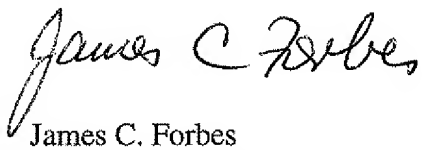
granted on that copending application" (Action, p. 26) is not a conclusion that can be reliably drawn at the present time. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '964 application issues as a patent.

8. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance. Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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